```
          7143 ALKYL
             1 ALKYLS
          7143 ALKYL
                 (ALKYL OR ALKYLS)
            73 HALIDE
            35 HALIDES
           108 HALIDE
                 (HALIDE OR HALIDES)
        592376 NITRILE
            33 NITRILES
        592376 NITRILE
                 (NITRILE OR NITRILES)
L2           0 ALKYL (L) HALIDE (L) NITRILE

=> FILE CAPLUS
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      34.78      34.99

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=> S HALIDE (L) NITRILE
        149293 HALIDE
        124649 HALIDES
        216923 HALIDE
                 (HALIDE OR HALIDES)
         55983 NITRILE
         26041 NITRILES
         70456 NITRILE
                 (NITRILE OR NITRILES)
L3        1484 HALIDE (L) NITRILE

=> S L3 AND Omega (1) alkyl
        171762 OMEGA
            12 OMEGAS
        171766 OMEGA
                 (OMEGA OR OMEGAS)
```

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        558176 ALKYL
          6206 ALKYLS
        560977 ALKYL
                 (ALKYL OR ALKYLS)
          5868 OMEGA (L) ALKYL
L4          11 L3 AND OMEGA (L) ALKYL

=> s l4 and dihalogen
           602 DIHALOGEN
            49 DIHALOGENS
           636 DIHALOGEN
                 (DIHALOGEN OR DIHALOGENS)
L5           0 L4 AND DIHALOGEN

=> d l4 ibib abs hitstr tot
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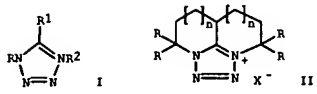
L4 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:240128 CAPLUS
DOCUMENT NUMBER: 126:330582
TITLE: Photochemical formation of heteromethylenecyclopropanes. Part 27. Annulated tetrazolium salts
AUTHOR(S): Quast, Helmut; Balthasar, Jurgen; Fuss, Andreas; Nahr, Uwe; Nudling, Wolfgang
CORPORATE SOURCE: Institut Organische Chemie, Univ. Wurzburg, Wuerzburg, D-97074, Germany
SOURCE: Liebigs Annalen/Recueil (1997), (4), 671-683
CODEN: LIARFV
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

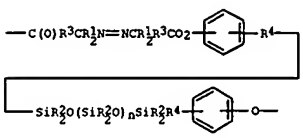


AB Lithiation of the annulated tetrazoles I [RR1 = (CH2)n, n = 3-4, R2 = electron pair] with BuLi yields the corresponding N-lithiotetrazoles which are allowed to react with alkyl halides. Alkylation at the α-C atoms occurs with MeI, Br(CH2)2Cl, and Br(CH2)3Br, while Cl(CH2)2Cl and Br(CH2)2Br give other products, e.g. I [RR1 = (CH2)3C(:X), (CH2)3CHBr; X = (CH2)2; R2 = electron pair]. Quaternization of I [RR1 = (CH2)n, n = 3-4, R2 = electron pair] with Me2SO4 affords mixts. of 1-methyl- and 2-methyltetrazolium salts (3:1-4:1) from which the hexafluorophosphates are obtained by crystallization. CF3SO3Me converts the omega.-azido nitriles N3(CH2)nCN (n = 3-5) into the N-methylnitrilium triflates [N3(CH2)nCH2C.tplbond.N+Me]CF3SO3- which immediately undergo an intramol. 1,3-dipolar cycloaddn. to afford the tetrazolium triflates I [RR1 = (CH2)n, n = 3-5, R2 = Me+CF3SO3-]. Cyclization of I [RR1 = (CH2)3CH(CH2)3Br, R2 = electron pair] by intramol. N-alkylation furnishes the bis-annulated tetrazolium bromide II (n = 1, R = H, X = Br). I [RR1 = (CH2)2CH(CH2)3Br, R2 = electron pair] rearranges into I [R = electron pair, R1R2 = (CH2)3CH(CH2)2Br]. The α-branched tetrazole I [R = electron pair, R1 = CH(CH2)2CClMe2, R2 = H] is synthesized from NCCH2CO2Et and Me2C:CHCH2Br. Double cyclization of the tetrazole afforded the bisannulated tetrazolium chloride II (n = 1, R = Me, X = Cl).

L4 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:485742 CAPLUS
DOCUMENT NUMBER: 123:170628
TITLE: Azo group-containing polymers and their manufacture
INVENTOR(S): Sugiura, Yoshihiko; Myaki, Yoshuki
PATENT ASSIGNEE(S): Tosoh Corp., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 07025998	A2	19950127	JP 1994-60698	19940330
JP 3341446	B2	20021105		
PRIORITY APPLN. INFO.:			JP 1994-60698 A	19940330
			JP 1993-109254	19930511

GI



AB The title radical-polymerizable azo group-containing polymers with number average mol. weight (Mn) 2000-500,000 containing repeating units I [R1 = H, lower alkyl, nitrile; R2 = H, halogen, (substituted) alkyl, Ph; R3-4 = C0-24 (branched) divalent hydrocarbon group; n = 0-500 integral number], useful for block copolymn., are manufactured by polycondensation of raw materials mainly composed of ≥2 phenolic OH-containing organopolysiloxanes and azo group-containing dicarboxylic acids or their acid halides. Thus, dissolving 8.4 g toluenesulfonic acid chloride in 20 mL dichloromethane (II), adding 10 mL pyridine, stirring, adding 5 mL DMF, stirring, mixing with 5.6 g 4,4'-azobis(4-cyanopentanoic acid) dispersed in 100 mL II, stirring at room temperature, mixing with 67 g α, ω -bis[2-(p-hydroxyphenyl)ethyl]polydimethylsiloxan e dissolved in 20 mL II, reacting at room temperature for 5 h, filtering, washing by MeOH, and evaporating gave 63 g azo group-containing polydimethylsiloxane ester with Mn 2400, number average mol. weight 47,000, viscosity 2000 P, and heat decomposition temperature 390° in yield 88%.

L4 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:172674 CAPLUS
DOCUMENT NUMBER: 110:172674
TITLE: Synthesis of ω-unsaturated acids
AUTHOR(S): Mirviss, Stanley B.
CORPORATE SOURCE: Stauffer Chem. Co., East. Res. Cent., Dobbs Ferry, NY, 10522, USA
SOURCE: Journal of Organic Chemistry (1989), 54(8), 1948-51
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 110:172674
AB A short, high-yield method for the synthesis of ω -unsatd. acids has been developed that precludes any double-bond migration or hydrogenation. Key is the coupling reaction between Grignards of . omega.-unsatd. alkyl halides and the bromomagnesium salt of ω -bromo fatty acids. The reaction has been successfully extended to ω -bromo nitriles . The use of ω -chloro acids or α-bromo acids gives lower yields of heterocoupling products and substantial homocoupling. A catalyst study shows Li2CuCl4 to yield the most heterocoupling of several catalysts tried for the chloro acids, and Ni(II) or Cu(I) are best for the α-bromo acids.

L4 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1970:131884 CAPLUS
DOCUMENT NUMBER: 72:131884
TITLE: Effect of alkyl side chains on some physical properties
AUTHOR(S): Cataldi, Mario T.
CORPORATE SOURCE: Fac. Farm. Bioquim., Univ. Sao Paulo, Sao Paulo, Brazil
SOURCE: Revista da Faculdade de Farmacia e Bioquimica da Universidade de Sao Paulo (1969), 7(2), 165-73
CODEN: RFBSAB; ISSN: 0014-6676
DOCUMENT TYPE: Journal
LANGUAGE: Portuguese
AB The effect of alkyl side chain length on molar refractivities and dipole moments was studied. Molar refractivities were studied for C3-C9, di-Me alkanedioates C1-C6 alkylbenzenes, C3-C9 α,. omega.-dichloroalkanes, 1,2-bicycloalkanediones from C5-C11, and Ge tetraalkylates from C1-C6. In all these series, there is a regular increase of the molar refractivity, on increasing the length of the alkyl chain, of .apprx.4.6 units for each CH2 added. Dipole moments were studied for alkyl halides from C1-C5, n-alkanethiols from C2-C7, nitriles from C1-C4, and α,. omega.-dibromoalkanes from C2-C5. For alkyl halides, thiols, and nitriles, dipoles moments increase steadily up to a given value and then remain constant For α,. omega.-dibromoalkanes, dipole moments alternately increase and decrease when adding one C to the chain.

L4 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1967:75417 CAPLUS
DOCUMENT NUMBER: 66:75417
TITLE: Heterolytic fragmentation. A class of organic reactions
AUTHOR(S): Grob, Cyril A.; Schiess, P. W.
CORPORATE SOURCE: Univ. St. Johanns, Basel, Switz.
SOURCE: Angewandte Chemie, International Edition in English (1967), 6(1), 1-15
CODEN: ACIEAY; ISSN: 0570-0833
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A review, with 119 references, of the preparation of olefins from alkanediols,
hydroxyalkylamines, decahydronaphthols, aldehydes, ketones, hexose hemiacetals, β-halo carboxylic acids, β-amino carboxylic acids, β-hydroxy carboxylic acids, arylethylenedicarboxylic acids, . omega.-amino alkyl halides, .omega.-(tertiary alkyl) alkyl halides, dihalo alkanes, and acid hydrazides, preparation of alkynes, such as benzyne, from unsatd. acids and benzoic acids, preparation of imines from N-halo amines and amine N-oxides, preparation of cyanic acids from amides, preparation of nitriles from ketoximes and α-halo anils, preparation of carbonyl compds. from alcs. and organic hydroperoxides, formation of N from azo compds., and formation of H3PO4 diesters from diaryl pyrophosphates.

L4 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1966:438454 CAPLUS
DOCUMENT NUMBER: 65:38454
ORIGINAL REFERENCE NO.: 65:7145h,7146a-h,7147a-h,7148a-f
TITLE: 1-[(3-, 2-, and 1-Indolyl)lower-alkyl-, lower-alkenyl-, and lower-alkynyl]piperidines
INVENTOR(S): Zenitz, Bernard L.
PATENT ASSIGNEE(S): Sterling Drug Inc.
SOURCE: 16 pp.; Continuation-in-part of U.S. 3,183,235 (CA 64, 5049c)
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3238215		19660301	US	19631017
PRIORITY APPLN. INFO.:			US	19631017

GI For diagram(s), see printed CA Issue.
AB The preparation is described of the title compds. (I), of their acid-addition and quaternary ammonium salts and of their intermediates. I are useful as hypotensive, antiinflammatory, and antibacterial agents and as sedatives, coronary dilators, psychic energizers, and tranquilizers. Thus, a solution of 4.48 g. 2-(3-indolyl)ethyl bromide and 6.3 g. 4-carbomethoxypiperidine in 200 ml. MeCN was refluxed 24 hrs. to give 3.8 g. 3-[2-(4-carbomethoxy-1-piperidyl)ethyl]indole, m. 110.4-11.8° (Me2CO-hexane). The following I (R1 = R2 = R3 = R4 = H) except where noted were prepared [R5, Z (at position 3- or 1-), and m.p. given]: 3-CO2Me, CH2CH2, 107.8-10.8°; 2-CO2Me, CH2CH2, 125.2-6.8°; 4-CO2Me, (CH2)3, 130.6-2.4°; 3-CO2Me, (CH2)3, 116.2-18.0°; 4-CONH2, CH2CH2, 182.6-4.0°; 4-CONHMe, CH2CH2, 166.8-9.2°; 4-CONHEt, CH2CH2, 166.4-8.6°; 4-CONEt2, CH2CH2, 139.2-40.4°; 4-CONHMe, (CH2)3, 139.8-40.6°; 4-CONHEt, (CH2)3, 147-8.2°; 4-CONH2, (CH2)3, 126.8-7.8°; 4-CONHMe, (CH2)3, 104.2-6.0°; 4-CONHEt, (CH2)3, 106.2-6.8°; 2-CONHEt, (CH2)3, 71.2-3.0°; 4-C7H13, CH2CH2, 143-3.8°; 4-CO2Me, CH2)3, 76-7.2°; 4-CO2Me, (CH2)3 (R3 = R4 = Me), 170.2-5.0°; 4-C7H13, (CH2)5, 125.6-7.2°; 4-C7H13, (CH2)3 (R3 = R4 = Me), 133-5°; 4-C7H13, CH2CH2, 94.2-5.6°.
I (Z = alkylenecarbonyl) (II) type compds. were prepared by reacting a 3- or 1-indolyl-lower alkanoic or alkenoic acid with a lower-alkyl haloformate in the presence of an acid acceptor at a temperature between -20° and 20° in an inert organic solvent. The indolyl-lower-alkane mixed anhydrides of the (1- or 3-indolyl)-lower-alkanoic and lower-alkenoic acids thus formed were reacted in situ with an appropriate piperidine at a temperature between -20° and 20°.
Thus, a solution of 6.85 g. isobutyl chloroformate in 125 ml. Me2CO was added dropwise with stirring to a solution of 10.16 g. γ-(3-indolyl)butyric acid and 11.0 g. of Et3N in 400 ml. Me2CO at -10 to -15°. To the mixture was added a solution of 8.9 g. of 4-carbomethoxypiperidine. The mixture was stirred 2 hrs., filtered and the filtrate concentrated to dryness. The residue was purified to give 11.4 g. of 4-carbomethoxy-1-[γ-(3-indolyl)butyryl]piperidine, m. 91.4-2.8° (EtOAc-hexane). The

L4 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
following II (2 at position 3- or 1-) were prepd. in a similar manner (R1 = R2 = R3 = R4 = H except where noted) (R5, the alkylene group in Z, and m.p. given): 4-COEt, CH2CH2, 123-5°; 3-CO2Me, CH2CH2, 107.4-8.4°; 2-CO2Et, CH2CH2, 86.8-8.4°; 4-CONH2, CH2CH2, 203.6-5.2°; 4-CONHEt, CH2CH2, 169.5-71.0°; 4-CONEt2, CH2CH2, 133.8-5.4°; 4-NHCOMe, CH2CH2, 188.8-90.2°; 4-CO2Me, CH2CH2, --, (yellow viscous oil); 4-CONEt2, CH2CH2, --, (oil); 4-NHCOMe, CH2CH2, 127.4-8.6°; 2-CH2C6H11, CH2CH2, --, (oil); 4-CH2C6H11, CH2CH2, 129.6-33.0°; 4-CH2C6H11, CH2CH2, --, (yellow viscous oil); 2-CH2C6H11, (CH2)4, 95.5-6.5°; 4-CH2C6H11, (CH2)5, 131.5-2.5°; 4-CH2C6H5, CH2CH2, 109.6-11.2°; 4-CH2C6H11, (CH2)4, --, (brown viscous oil); 4-CH2C6H11, CH2CH2, (R1 = 5-Me) 143.2-4.5°; 2-CH2C6H11, CH2CH2, (R1 = 5-F), 158.8-60.2; 4-CH2C6H11, CH2CH2, (R1 = 5-F), 120.4-2.2°; 4-CH2C6H11, (CH2)3, (R1 = 5-F), 149.8-51°; 4-CH2C6H5, CH2CH2, (R1 = 5-F), 135.0-6.4°; 4-CH2C6H11, CH2CH2, (R1 = 5-MeO), --, (brown viscous oil); 4-CH2C6H11, CH2CH2, (R1 = PhCH2O), 148-9°; 4-CH2C6H11, CH2CH2, (R1 = F3C), 160°; 4-CH2C6H11, (CH2)3, (R1 = F3C), 154.5-155.3°; 4-CH2C6H5, CH:CH, 118-20°; 4-CO2CH2CHMe2, CH2CH2, 107.8-9.2°; 3-CONHEt, CH2CH2, 157.4-8.4°; 2-CO2CEt, CH2CH2, 95.2-7.2°; 3-CONHEt, CH2CH2, 111.2-12.8°; 4-CO2Me, CH2CH2, 123.2-4.2°. Also prepd. in a similar manner was 4-cyclohexylmethyl-1-[β-(5-methylthio-3-indolyl)propionyl]piperidine.
I were also prepd. by reacting with LiAlH4, a resp. II in an inert org. solvent at a temp. of 0-65°. The following I were thus prepd. (R1 = R2 = R3 = R4 = H except where noted) [R5, Z (at position 3- or 1-), base or salt, and m.p. given]: 4-CH2OH, (CH2)4, base, 164.2-5.0°; 4-CH2OH, (CH2)3, base, 151.8-3.2°; 3-CH2OH, (CH2)3, base, 160.8-3.8°; 2-CH2OH, (CH2)3, base, 151.4-4.6°; 4-CH2NH2, (CH2)3, base, 115.6-16°; 4-CH2NHEt, (CH2)3, 2HCl, 245.4-7.2°; 4-CH2NEt2, (CH2)3, 2HCl, 202.4-8.0°; 4-NHEt, (CH2)3, 2HCl, 277.2-9.2°; 4-CH2OH, (CH2)3, base, 85.8-87°; 4-CH2NEt2, (CH2)3, 2HCl, 219.4-20.6°; 4-NHEt, (CH2)3, 2HCl, 264.6-6.2°; 2-CH2C6H11, (CH2)3, base, 113.6-15.4°; 2-CH2C6H11, (CH2)3, base, 124-6.8°; 4-CH2C6H11, (CH2)3, base, 109.6-11.8°; 4-CH2C6H11, (CH2)3, base, 114.8-16.6°; 2-CH2C6H11, (CH2)4, EtSO3H, 137.6-8.6°; 4-CH2C6H11, (CH2)4, base, 96.6-8°; 2-CH2C6H11, (CH2)5, EtSO3H, 124.2-6.0°; 4-CH2C6H11, (CH2)5, p-tosylate, 177.6-80° 4-CH2C6H11, (CH2)6, base, 82-3.8°; 4-CH2Ph, (CH2)3, base, 122-4°; 4-CH2Ph, (CH2)4, HCl, 192.8-5.2°; 2-CH2C6H11, (CH2)3, HCl, 151.6-4.2°; 4-CH2C6H11, (CH2)3, HCl, 208.4-10.0°; 4-CH2C6H11, (CH2)3, base, --, (b0.00075 180.5-4.0°); 4-CH2C6H11, (CH2)5, HCl, 168.8-72.2°; 4-CH2C6H11, (CH2)3, base, 86.8-104.5°; 2-CH2C6H11, (CH2)3, base, 120.2-2.2°; 4-CH2C6H11, (CH2)3, base, 104.4-6.6°; 4-CH2C6H11, (CH2)4, base, 119.2-20°; 4-CH2Ph, (CH2)3, base, 116.8-17.8°; 4-CH2C6H11, (CH2)3, base, 118-19.8°; 4-CH2C6H11, (CH2)3, base, 105.2-6.4°; 4-CH2C6H11, (CH2)3, base, 95-6°; 4-CH2C6H11, (CH2)4, HCl, 208.6-10.8°; 4-CH2C6H11, (CH2)3, base, 118.6-20.4°; 4-CH2C6H11, (CH2)4, base, 143.2-5.8°; 4-CH2C6H11, CH:CHCH2, base, 149-52.6°; 4-CH2Ph, CH:CHCH2, base, 131.8-4.4°. In a similar manner were prepd. the following I·2HCl [R1 = R2 = R3 = R4 = H; Z = (CH2)2] (R5 and m.p. given): 4-NHEt, 259.6-62°; 4-CH2NHEt, >290°. Also thus prepd. were 2-[2-[2-(N-allylaminomethyl)-1-piperidyl]ethyl]indole and 3-[3-(4-cyclohexylmethyl-1-piperidyl)propyl]-5-methylthioindole, m. 130.8-2.6° (EtOAc-hexane). III were prepd. by reacting an indole with an oxalyl halide at -20 to 25° in an inert org. solvent to give the corresponding 3-indolyloxalyl halide which

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was then reacted with an appropriate piperidine in an inert org. solvent at -5 to 65° in the presence of an acid-acceptor. Thus, to a stirred soln. of 9.3 g. 4-carbomethoxypiperidine in 200 ml. tetrahydrofuran (THF) was added dropwise over a period of 45 min. a soln. of 14.3 g. 3-indolyloxalyl chloride at -10 to -20°. The mixt. was kept 12 hrs. at 4° and then filtered. The filtrate was evapd. to dryness in vacuo leaving a reddish oil, which was purified to give 10 g. 4-carbomethoxy-1-(3-indolyloxalyl)piperidine, m. 135.4-36° (EtOAcC6H14). III (R4 = H) listed in the table were similarly prepd. R1, R3, R5, M.p.; H, H, 2-CH2C6H11, (brown viscous oil); H, Me, 4-CH2C6H11, 197.5-200°; 5-MeO, H, 2-CH2C6H11, 134-6°; 5-MeO, H, 4-CH2C6H11, 164.5-6°; 5,6-di-MeO, H, 4-CH2C6H11, 216-18°; 5-F, H, 4-CH2C6H11, 169.2-71.8°; 5-MeS, H, 4-CH2C6H11, 156-8°; 5-PhCH2O, H, 2-CH2C6H11, 174-6°; 5-PhCH2O, H, 4-CH2C6H11, 168-9°; I were prepd. from III by treating them with LiAlH4 in an inert org. solvent at a temp. between 0 and 65°.
Thus, a stirred slurry of 15.24 g. LiAlH4 in 300 ml. dry THF was added dropwise over a period of 1 hr. to a soln. of 35 g. 2-cyclohexylmethyl-1-(3-indolyloxalyl)piperidine in 450 ml. THF. The mixt. was refluxed 4 hrs., cooled and treated dropwise with stirring with 32 ml. H2O. The mixt. was filtered and the combined filtrates were evapd. to dryness to give 16.7 g. 3-[2-(2-cyclohexylmethyl-1-piperidyl)ethyl]indole, m. 151.6-2.8° (EtOAc-C6H14). I [R3 = R4 = H, Z = 3-(CH2)2] listed in the table were prepd. in a similar manner. R1, R5, M.p.; 5-OMe, 2-CH2C6H11, 140.8-3.4°; 5-OMe, 4-CH2C6H11, 98.4-9.8°; 5,6-di-MeO, 4-CH2C6H11, 131-2°; 5-F, 4-CH2C6H11, 140.6-1.8°; 5-SMe, 4-CH2C6H11, 134.6-5.8°; 5-PhCH2O, 2-CH2C6H11, 81-5.2°; 5-PhCH2O, 4-CH2C6H11, 115-16.2° Also prepd. was I (R1 = R2 = R4 = H, R3 = Me, R5 = 4-C7H13), Z = 3-CH2CH2, m. 142.4-4.2°. Also prepd. in a similar manner was 3-[2-(4-cyclohexylmethyl-1-piperidyl)ethyl]-5-benzylthioindole, m. 121.4-3.4° (MeOH). I were also prepd. by treating an appropriate substituted phenylhydrazine with an appropriate 1-(N-formyl-lower-alkyl)-substituted piperidine or 1-(.omega. .-lower-alkanoyl-lower-alkyl)-substituted piperidine. Thus, a mixt. of 36.3 g. 2-cyclohexylmethylpiperidine, 48.2 g. 1-chloro-4-pentanone and 83.5 g. K2CO3 in 100 ml. PhMe was heated with stirring 6 hrs. The mixt. was dild. with 1.5 l. Et2O, filtered, the filtrate evapd. to dryness and the residue oil distd. in vacuo to give 25.2 g. 1-(3-acetylpropyl)-2-cyclohexylmethylpiperidine, (IV) b0.17 117-24°. A mixt. of 10.6 g. IV, 4.35 g. phenylhydrazine, and 15.9 ml. 7.6N ethanolic HCl in 150 ml. EtOH was refluxed 20 hrs. The solid which sepd. on cooling was collected, suspended in CH2Cl2, and extd. with dil. NH4OH. The org. layer was evapd. to dryness and gave 5.9 g. 2-methyl-3-[2-(2-cyclohexylmethyl-1-piperidyl)ethyl]indole, m. 125.4-6.6° (EtOAcC6H14). I [R2 = R4 = H, Z = 3-(CH2)2] listed in the table were prepd. in a similar manner. I, in which Z is lower-alkynylene, were prepd. by reacting a 3-propynylindole with CH2O and an appropriate substituted piperidine in an inert org. solvent at 50-150°. R1, R3, R5, Base or salt, M.p.; 5,6-di-MeO, H, 2-CH2C6H11, base, 109.8-14.2°; 5,6-di-MeO, Me, 2-CH2C6H11, base, 100.6-6.2°; 5,6-di-MeO, Me, 4-CH2C6H11, base, 123.8-5.2°; 5,6-MeO, Me, 4-CH2C6H11, HCl, 262-4° Thus, to a mixt. of 9.6 g. Mg turnings in 40 ml. anisole was added 64 g. EtI. A soln. of 31.2 g. indole in 40 ml. anisole was added dropwise with stirring and cooling over a period of 15 mins. The mixt. was stirred 0.5 hr. at room temp., then chilled to 0-5° and treated dropwise over a period of 0.5 hr. with a soln. of 61 g. propargyl bromide in 40 ml. anisole. The mixt. was decompd. with 24 ml. AcOH in 200 ml. icewater and yielded 11.7 g.

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3-(2-propynyl)indole, (V) b1.4 125.5-26°. A mixt. of 4.6 g. V, 6 g. 4-cyclohexylmethylpiperidine and 1 g. paraformaldehyde in 20 ml. dioxane was heated on a steam bath 11 hrs. The solvent was then removed in vacuo to give 2.6 g. 3-[4-(4-cyclohexylmethyl-1-piperidyl)-2-butynyl]indole, m. 65.8-8.2°. I, II, and III where R5 is aminocarbamyl were prepd. by reacting the resp. compds. of I, II, and III where R5 is carbo-lower-alkoxy with a molar excess of 100% hydrazine hydrate at 80-120°. Thus were prepd. 3-[2-(4-aminocarbamyl-1-piperidyl)ethyl]indole, m. 164.6-66° (CHCl3-C6H14), and 3-[2-(2-aminocarbamyl-1-piperidyl)ethyl]indole, m. 138.4-9.8° (CHCl3-C6H14). I, II, and III where R5 is N-lower-alkylidine hydrazono were prepd. by reacting the resp. compds. of I, II, and III where R5 is aminocarbamyl with a lower aliphatic aldehyde or di-lower-alkyl ketone at a temp. from 50-150°. Thus was prepd. 3-[2-(4-isopropylidenehydrazono-1-piperidyl)ethyl]indole, m. 184-6.8° (EtOAc). I, II, and III where R5 is N-lower-alkylaminocarbamyl were prepd. by reducing with H over a catalyst the resp. compds. of I, II, and III where R5 is N-lower-alkylidene hydrazono. The reaction was carried out in an inert org. solvent at a temp. of 25-75° and at H pressures between 50-70 psi. Thus was prepd. 3-[2-(4-isopropylaminocarbamyl-1-piperidyl)ethyl]indole, m. 151.4-3.8° (CHCl3-C6H14). The following pentachlorobenzochloride of I (R1 = R2 = R3 = H; R3 = Me; R5 = 4-CH2C6H11; Z = (CH2)3)(VI) was prepd. by heating a soln. of 7.05 g. 3-[3-(4-cyclohexylmethyl-1-piperidyl)propyl]-2-methylindole with 7.45 g. 2,3,4,5,6-pentachlorobenzyl chloride in 250 ml. MeCN under reflux 14 hrs. The solvent was evapd. and the residual oil was boiled with 450 ml. Me2CO to give 4.1 g. VI, m. 129.2-47.2° (iso-PrOH). The following I (R1 = 5-HO; R2 = R3 = R4 = H; R5 = CH2C6H11) were prepd. from the corresponding I (R1 = 5-PhCH2O) by redn. with H over Pd-C as catalyst (Z and m.p. given): (CH2)3, 169.4-70.4°; (CH2)2, 171.2-2.4°. The 3-indolyl-lower-alkanoic acids, (VII), used as intermediates in the prepn. of II were prepd. by reacting an appropriate benzenediazonium chloride with an appropriate 2-carbo-lower-alkoxycycloalkanone followed by hydrolysis with aq. Na2CO3 to give the phenylhydrazone of an α-oxodicarboxylic acid ester or half ester, which was then cyclized under conditions of the Fischer indole synthesis. Thus was prepd. 4-fluorophenylhydrazone of ethyl α-oxopimelic acid half ester, m. 143-5° (EtOAc-C6H14) which was then cyclized to γ-(2-carboxy-5-fluoro-3-indolyl)butyric acid, m. 230.2-1.2°. In a similar manner were prepd. the following VII (R2 = H, R3 = CO2H) (R1, Z, and m.p. given): 5-CF3, CH2CH2, 229.6-9.8°; 5-PhCH2O, CH2CH2, 185-7°; 5-CF3, (CH2)3, 227.5-8.0°; 5-F, CH2CH2, 236.2-7.4°; 5-Me, CH2CH2, 219.7-19.8°; 5-PhCH2O, (CH2)3, 199-201.2°. Decarboxylation of VII (R3 = CO2H) over a Cu-quinoline mixt. afforded the corresponding VII (R3 = H). Thus were prepd. the following VII (R2 = R3 = H), (R1, Z, and m.p. given): 5-F, (CH2)3, 126.4-7.2°; 5-CF3, CH2CH2, 84-90°; 5-PhCH2O, CH2CH2, 86-95°; 5-CF3, (CH2)3, 158.6-9.6°; 5-F, CH2CH2, 121.2-3.0°; 5-Me, CH2CH2, 137-9°; 5-PhCH2O, (CH2)3, 159-61°. VII (R1 = R2 = H, R3 = Me) were prepd. by alkylation of an appropriate indole Mg halide (prepd. by reacting the indole with a lower-alkyl Mg halide) with an ω -halo-lower-alkyl nitrile. Thus were prepd. γ-(2-methyl-3-indolyl)butyronitrile, b0.0002 159-60°, δ-(2-methyl-3-

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indolyl)valeronitrile, b.0.001 158-60°, γ-(2-methyl-3-indolyl)butyric acid, m. 91.2-93° (MeOH-H2O), and δ-(2-methyl-3-indolyl)valeric acid. Also prepd. was β-(2,5-dicarboxy-3-indolyl)propionic acid, m. 293.6-4.2° (aq. EtOH) from the corresponding ethyl ester. The indolyl-lower-alkyl halides used as intermediates for the prepn. of I were prepd. by redn. of a 1-, 2-, or 3-indolyl-lower-alkanoic acid with LiAlH4 and conversion of the resulting alc. to the corresponding halide with FX3 or SO2X (where Z is a CH2CH2 group) or with p-MeC6H5SO2X in C5H5N at -5° to +15° (where Z contains more than 2 linear C atoms).

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PATENT ASSIGNEE(S): A. H. Robins Co., Inc.
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GI For diagram(s), see printed CA Issue.

AB The title compds. are analeptics, hypotensives, or both. The starting acetonitriles (I) required for the synthesis of the title compds. were prepared as follows. Ph2CHCN (193 g.) was added dropwise at 50° to a stirred suspension of 43 g. NaNH2 in 1 l. dry PhMe, refluxed 4 hrs., treated at a rapid dropwise rate with 162 g. 1-iso-butyl-3-chloropyrrolidine and refluxed with stirring 3 hrs. The cooled mixture was extracted with N HCl and the separated aqueous plus oil layers made basic with NaOH and extracted with Et2O to yield on removal of the Et2O, 250 g. α-(1-isobutyl-3-pyrrolidinyl)-α,α-diphenylacetonitrile (I, A = R = Ph, R1 = iso-Bu) (Ia), b0.15 190-200°, m. 76-7°. The following I nitriles were similarly prepared starting with the appropriate 1-substituted-3-chloropyrrolidine and the selected α,α-acetonitrile (given A, R, R1): allyl, Ph, iso-Pr; C6H11, C6H11, allyl; Me, Me, Ph; PhCH2, Ph, iso-Pr; Ph, 1-iso-Pr-3-pyrrolidinyl, iso-Pr; Ph, 2 (or 3)-thienyl, iso-Pr; p-MeOC6H4, Ph, iso-Pr; m-ClC6H4, Ph, iso-Pr; o-MeC6H4, Ph, iso-Pr; Me, cyclopentyl, iso-Pr; Ph, 2-piperidinyl, Me; Ph, 4-N-methylpiperidinyl; and the 5-Me, 4-Me, 3-Me, and 2-Me derivs. of I (A = R = Ph, R1 = iso-Pr); Ph, Ph, Me, m. 81-2°; Ph, Ph, Et, m. 83-4°; Ph,Ph, iso-Pr, m. 73-4°; Ph, Ph, iso-Bu, m. 76-7°; Ph, Ph, cyclohexyl, b0.005 195-200°; Ph, Ph, MeC6H4, b0.01 215-18°; Ph, pyridyl, MeC6H4, b0.08 200-10°; Ph, pyridyl, iso-Bu, b0.07 161-5°; Ph, pyridyl, cyclohexyl, b0.05 200-8°; Ph, pyridyl, Bu, b0.08 170-5°; Ph, pyridyl, iso-Pr, m. 107-9°; Ph, pyridyl, Et, m. 110-19°; Ph, pyridyl, Me, b0.07 148-51°; p-MeOC6H4, pyridyl, Me, b0.08 170-3°; p-MeOC6H4, pyridyl, Et, b0.08 200-2° p-MeOC6H4, pyridyl, iso-Pr, b0.05 190°; Ph, iso-Pr, Et, b0.15-0Middot;20 121-30°; Ph, Ph, iso-Pr, b0.002 124-5°; Ph, Me, iso-Pr; Ph, cyclopentyl, iso-Pr, b0.005 147-9°; Ph, cyclohexyl, iso-Pr, b0.001 169-75°. The 1,3,3,4-tetra-substituted-2-pyrrolidinones were prepared from the acetonitriles as indicated in the diagram, by first hydrolyzing the nitrile with strong mineral acid at high temperature to give the corresponding acid, and converting the product (II) with an acyl halide to the corresponding mixed anhydride (III). This was rearranged by heating to the 4-(ω-haloalkyl)-2-pyrrolidinone (IV). Thus, a solution of 100 g. Ia in 500 g. 70% H2SO4 was heated 48 hrs. at 130-40°, poured onto ice, made basic with NaOH, extracted with CHCl3, and the CHCl3 solution acidified with HCl, dried, and concentrated The

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refluxed with 500 ml. SOCl2 hrs. to yield 69 g. 4-(β-chloroethyl)3,3-diphenyl-1-isobutyl-2-pyrrolidinone (IV, Q = Cl, A = R = Ph, R1 = iso-Bu) (IVa), m. 113-13.5°. The following IV derivs. were similarly prepd. from the appropriate nitriles (given Q, A, R, R1): Cl, Ph, Ph, PhCH2; Cl, Ph, Ph, Me; Cl, Ph, Ph, cyclohexyl; Cl, Ph, Ph, Et; Cl, Ph, Ph, iso-Pr; Cl, Me, Ph, iso-Pr. Replacing the SOCl2 with SOBr2 or PBr3 as the halogenating agent yielded the corresponding 4-bromoalkyl compds. Thus, a soln. of 31.5 g. of crude α-(1-Et-3-pyrrolidyl)-α,α-diphenylacetic acid-HCl (II, A = R = Ph, R1 = Et) (IIa) (obtained from the nitrile as above) and 20 ml. PBr3 in 70 ml. CHCl3 was refluxed 13 hrs. to yield 4 g. IV (Q = Br, A = R = Ph, R1 = Et), m. 129-30°. A mixt. of 2.3 g. α,α-diphenyl-α(1-isopropyl-3-pyrrolidinyl)acetic acid (IIb) and 2.1 g. NaI was refluxed in 25 ml. dry MeCOEt and 2 ml. Ac2O 1.5 hrs. to yield 2.15 g. IV (Q = I, A = R = Ph, R1 = iso-Pr) (IVb), m. 143-6°. A mixt. of 25 g. IV (Q = Cl, A = R = Ph, R1 = iso-Pr) (IVc) and 12.5 g. NaI in 200 ml. Me2CO was refluxed 18 hrs. to yield 24.9 g. IVb. A mixt. of I (A = R = Ph, R1 = iso-Pr) in 120 g. 70% H2SO4 was heated 64 hrs. at 128-34°, poured into 100 g. ice, made strongly basic with 50% NaOH, the H2O removed in vacuo, and the residue extd. with 2 + 250 ml. boiling EtOH. The residue from the EtOH exts. was dissolved in 400 ml. H2O and treated with AcOH to ppt. 34.1 g. IIb, m. 248-50° (decompn.) (HCONMe2). IIa, m. 136-9° (decompn.) (EtOH-C6H6) was similarly prepd. from I (A = R = Ph, R1 = Et). A suspension of 2.5 g. IIa in 100 ml. dry CHCl3 was treated with dry HCl till soln. was complete, 2 ml. SOCl2 added, and the mixt. refluxed 2 hrs. to yield 2 g. IV (Q = Cl, A = R = Ph, R1 = Et) (IVd). In the manner of the preceding examples but starting with the appropriate acetonitrile, or the corresponding acid, or intermediate amide, the following IV compds. were prepd. (given Q, A, R, R1): Cl, allyl, Ph, iso-Pr; Cl, cyclohexyl, cyclohexyl, allyl; Cl, Me, Me, Ph; Cl, PhCH2, Ph, iso-Pr; Cl, Ph, 1-iso-propyl-3-pyrrolidinyl, iso-Pr; Cl, Ph, 2- or 3-thienyl, iso-Pr; Cl, Ph, 2- or 3-thienyl, iso-Pr; Cl, Ph, p-MeOC6H4, iso-Pr; Cl, Ph, m-ClC6H4, iso-Pr; Cl, Ph, o-MeC6H4, iso-Pr; Cl, Me, cyclopentyl, iso-Pr; CH2Cl, Ph, 2-piperidyl, Me; CH2Cl, Ph, 4-N-methylpiperidyl, iso-Pr; Cl, Ph, Ph, Me; Cl, Ph, Ph, Et; Cl, Ph, Ph, iso-Bu; Cl, Ph, Ph, cyclohexyl; Cl, Ph, Ph, PhCH2; Cl, Ph, 2-pyridyl, PhCH2; Cl, Ph, 2-pyridyl, iso-Bu; Cl, Ph, 2-pyridyl, cyclohexyl; Cl, Ph, 2-pyridyl, Bu; Cl, Ph, 2-pyridyl, iso-Pr; Cl, Ph, 2-pyridyl, Et; Cl, Ph, 2-pyridyl, Me; Cl, p-MeOC6H4, 2-pyridyl, Me; Cl, p-MeOC6H4, 2-pyridyl, Et; Cl, p-MeOC6H4, 2-pyridyl, iso-Pr; Cl, iso-Pr, Ph, Et; Cl, Ph, iso-Pr, iso-Pr; Cl, Me, Ph, iso-Pr; Cl, cyclopentyl, Ph, iso-Pr; Cl, cyclohexyl, Ph, iso-Pr; CH2CH2Cl, Ph, Ph, iso-Pr. In addn. the following compds. were also similarly prepd.: 4-(γ-chloropropyl)-3-phenyl-3-(2-piperidinyl-1-methyl-2-pyrrolidinone; 4-(γ-chloropropyl)-3-phenyl-3-[4-(N-methylpiperidinyl)]-1-isopropyl-2-pyrrolidinone; 4-(γ-chloro-2-propyl), 4-(δ-chloro-2-butyl), 4-(γ-chlorobutyl), 4-(γ-chloro-β-methylpropyl), 4-(β-chloropropyl), 4-(β-bromopropyl), 4-(β-chloromethyl)-4-methyl, and 4-(β-chloroethyl)-5-methyl-3,3-diphenyl-1-isopropyl-2-pyrrolidinone. A soln. of 73 g. α- (1 -isopropyl-3-pyrrolidinyl)-α-cyclopentyl-α-phenylacetamide (V, A = Ph, R = cyclopentyl, R1 = iso-Pr) (Va) in 200 ml. AcOH was satd. with HCl and 47.9 g. BuNO2 was added slowly below the surface during 2 hrs. with stirring at 30°. The mixt. was kept at room temp. 15 hrs., 3 hrs. at 100° and then concd. in vacuo. The residue in CHCl3 was washed with H2O and again concd. in vacuo. This residue was refluxed with 500 ml. SOCl2 2 hrs. to yield 57.3 g. IV (Q = Cl, A = cyclopentyl, R = Ph, R1 = iso-Pr), b0.03 178-80°, m. 74.5-7.5° (ligroine). The following IV compds. were similarly prepd. from the corresponding acid amides (given Q, A, R,

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R1): Cl, iso-Pr, Ph, iso-Pr; Cl, cyclohexyl, Ph, iso-Pr. A soln. of 150 g. I (A = cyclopentyl, R = Ph, R1 = iso-Pr) in 800 g. 70% H2SO4 was heated 48 hrs. at 147°, poured onto ice, made basic with 50% NaOH, and extd. with CHCl3 to yield 105 g. Va, b0.2 221-5°. The following amides were similarly prepd. (given A, R, and R1, m.p. (or b.p.): iso-Pr, Ph, iso-Pr, b0.05 175-80°; cyclohexyl, Ph, iso-Pr, b0.14 208-16°; Ph, Ph, Me, 154-5°; Ph, Ph, Et, 141-2°; Ph, Ph, iso-Pr, 141.5-42°; Ph, Ph, cyclohexyl, 119-22°; Ph, 2-pyridyl, Et, 160-1°; Ph, 2-pyridyl, Me, 150-3°; Ph, 2-pyridyl, iso-Pr, 127.5-33°; Ph, 2-pyridyl, Bu, 108-11°. The following IV derivs. were made from I via the amides V, the acids II, followed by rearrangement of the acyl halides (given Q, A, R, R1, m.p.): Cl, Ph, Ph, Me, 140-1°; Cl, Ph, Ph, Et, 117-19°; Br, Ph, Ph, Et, 129-30°; Cl, Ph, Ph, iso-Pr, 106-8°; Cl, Me, Ph, iso-Pr, 102-4°; Cl, Ph, iso-Pr, iso-Pr, 95-6°; Cl, Ph, cyclopentyl, iso-Pr, 74.5-75°; Cl, Ph, cyclohexyl, iso-Pr, 109-11° Cl, Ph, Ph, iso-Bu, 113.5-14.5°; Cl, Ph, Ph, cyclohexyl, 151-2°; Cl, Ph, Ph, PhCH2, 110°; I, Ph, Ph, iso-Pr, 147-9°; CH2Cl, Ph, Ph, iso-Pr, 85-6.5°; Cl, 3-pyridyl, Ph, Et, 100-3°; Cl, Ph, Ph, Et, 150-3°, (side chain CHCH3CH2); Cl, Ph, Ph, Et, 141-2°, (side chain CH2CHCH3). A mixt. of 18 g. AcONa and 70 g. IVc in 500 ml. HCONMe2 was refluxed with stirring 15 hrs., partitioned between 500 ml. H2O and 500 ml. CHCl3, and sepd. to yield from the CHCl3 layer 54 g. IV (Q = OAc, A = R = Ph, R1 = iso-Pr) (IVe), m. 91-4°. A mixt. of 2.5 g. IIb and 20 ml. AcOH was refluxed 5 hrs. to yield 1.65 g. IVe. A soln. of 34 g. IVe and 4 g. NaOH in 450 ml. EtOH and 10 ml. H2O was refluxed with stirring 1 hr., concd. in vacuo, and partitioned between CHCl3 and H2O to yield from the CHCl3 layer 22 g. IV (Q = OH, A = R = Ph, R1 = iso-Pr),m. 180-2°(aq.EtOH). A soln. of 16.2 g. NaHS.2H2O and 30 g. IVc in 400 ml. 85% EtOH was refluxed 7 hrs., concd., and the residue partitioned between CHCl3 and H2O to yield from the CHCl3 layer 17 g. IV (Q = SH, A = R = Ph, R1 = iso-Pr) (IVf), b0.5 220-30°, m. 104-7° (EtOH-H2O). A soln. of 11.5 g. MeBr in 200 ml. EtOH was added to a soln. of 20 g. IVf in 200 ml. EtOH contg. 1.5 g. Na and stirred at room temp. 4 hrs. to yield 20 g. IV (Q = SMe, A = R = Ph, R1 = iso-Pr),m. 123-5°. A soln. of 34g. IVc in 200 ml. abs. EtOH contg. 2.5 g. Na was heated in a closed system 16 hrs. at 140° to yield 27.5 g. IV (Q = OMe, A = R = Ph, R1 = iso-Pr), m. 105-6° (MeOH-H2O). PhONa (prepd. from 8.3 g. PhOH and 2 g. Na in 300 ml. EtOH) and 30 g. IVc in 100 ml. EtOH was refluxed for 7 hrs. to yield 17 g. IV (Q = OPh, A = R = Ph, R1 = iso-Pr), m. 104-6° (EtOH-H2O). A soln. of 25 g. IVc, 25 g. KBr, and 60 ml. 48% HBr in 250 ml. AcOH was refluxed with stirring 2 hrs., treated with 60 g. Zn dust in small portions, then with 60 ml. 48% HBr (dropwise during 2 hrs.), and allowed to stand overnight at room temp. to yield 9 g. IV (Q = H, A = R = Ph, R1 = iso-Pr), m. 95-7° (aq. EtOH). The corresponding R1 = iso-Bu compd., m. 94.0-6.5° was similarly prepd. from IVa. In the manner of the preceding examples, the complete list of ω-chloroalkyl compds. given above were converted to the corresponding ω-hydroxyalkyl compds. and 4-ω-acyloxyalkyl compds. The following are representative of this group of compds. (given Q, A, R, R1, and m.p.): OAc, Ph, Ph, iso-Pr, 91-4°; SH, Ph, Ph, iso-Pr, 104-7°; SMe, Ph, Ph, iso-Pr, 123-5°; OMe, Ph, Ph, iso-Bu, 86-7°; OMe, Ph, Ph, iso-Pr, 105-6°; PhO, Ph, Ph, iso-Pr, 104-6°; OH, Ph, Ph, iso-Pr, 180-2°; CH2OH, Ph, Ph, iso-Pr,

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142-3°; o-MeOC6H4, Ph, Ph, iso-Pr, 135-7°; CO2C5H4N, Ph, Ph, iso-Pr, 104-5°; o-HOC4H4CO2, Ph, Ph, iso-Pr, 111-12°. A mixt. of 342 g. IVc and 75 g. NaCN in 1 l. HCONMe2 was heated with stirring 4 hrs. at 100° and poured into ice-H2O to yield 288 g. IV (Q = CN, A = R = Ph, R1 = iso-Pr) (IVg), m. 150-1°. A mixt. of 94 g. IVg and 500 ml. 70% H2SO4 was heated with stirring 24 hrs. at 80-90° and poured into ice-H2O to yield 93% IV (Q = CO2H, A = R = Ph, R1 = iso-Pr) (IVh), m. 175-6°. A suspension of 144 g. IVh in 500 ml. dry C6H6 was treated at 20-5° with 97.5 g. SOCl2 and refluxed 1 hr. to yield IV (Q = COCl, A = R = Ph, R1 = iso-Pr) (IVi), m. 141.5-3.5°. A soln. of 30 g. IVi in 300 ml. dry EtOH was added to a soln. of 2.05 g. Na in 200 ml. EtOH and stirred overnight at room temp. to yield 23 g. of the ester IV (Q = CO2Et, A = R = Ph, R1 = iso-Pr) (IVj), m. 84-5° (70% MeOH). IVi (54 g.) was added portionwise with vigorous stirring to cold concd. NH4OH to yield 46 g. IV(Q = CONH2, A = R = Ph, R1 = iso-Pr), m. 203.5-5.0°. A soln. of 7.75 g. MeNH2 in 150 ml. C6H6 was added dropwise with stirring to a suspension of 25 g. IVi in C6H66 and refluxed 1 hr. to yield 84% IV (Q = CONHMe, A = R = Ph, R1 = iso-Pr), m. 170-1°. IV (Q = CONMe2, A = R = Ph, R1 = iso-Pr), m. 149-50° was similarly prepd. A mixt. of 10 g. CdCl2 and Grignard reagent (prepd. from 10.9 g. EtBr and 2.4 g. Mg in 100 ml. dry Et2O) was refluxed 1 hr., the Et2O distd., 200 ml. dry PhMe added the soln. heated 30 min. at 90°, cooled to 60° , a soln. of 30 g. IVi in 150 ml. PhMe added dropwise, the mixt. stirred 2 hrs. at 85° and hydrolyzed with H2O and 6N HCl, the PhMe layer washed with dil. NaOH, dried, and distd. to yield 8 g. IV (Q = COCH2CH3, A = R = Ph, R1 = iso-Pr), b0.2 220-50° m. 120-2.5°, (60% EtOH). To a boiling soln. of 5 g. IVj in 50 ml. abs. EtOH was added as rapidly as possible 2 g. Na and the mixt. heated to reflux; 30 ml. H2O was added, the mixt. refluxed 1 hr., and the solvent removed to yield IV (Q = CH2OH, A = R = Ph, R1 = iso-Pr) (IVk), m. 140-1.5° (50% EtOH). To a suspension of 10 g. NaBH4 was added rapidly with stirring 25 g. IVi in 200 ml. dry dioxane and the mixt. refluxed 4 hrs. to yield 10 g. IVk. A soln. of 7.4 g. SOCl2 in 50 ml. CHCl3 was added dropwise to a soln. of 10.5 g. IVk and 4.9 g. C5H5N in 100 ml. CHCl3 with stirring and ice bath cooling. The mixt. was refluxed 5 hrs., cooled, and treated with 50 ml. 3N HCl to yield 8 g. IV (Q = CH2Cl, A = R = Ph, R1 = iso-Pr) (IVl), m. 85.0-6.5° (60% EtOH). A mixt. of 3.9 g. NaCN and 9.2 g. IVl in 100 ml. HCONMe2 was refluxed for 17 hrs. to yield 5 g. IV (Q = CH2CN, A = R = Ph, R1 = iso-Pr), m. 126-7° (iso-PrOH). The list of 4-(ω-haloalkyl)-2-pyrrolidinones given previously were converted in the manner of the preceding examples to the nitriles, acids, acid halides , acid esters, and acid amides. The following representative compds. of this group were also thus prepd. (R = A = Ph, R1, and m.p. given): CN, iso-Pr, 150.5-1.0°; CO2H, iso-Pr, 175-6°; CONMe3, iso-Pr, 149-50°; CONH2, iso-Pr, 203.5-5.0°; CONHMe, iso-Pr, 170-1°; hexamethyteniminocarbonyl, iso-Pr, 144-5°; N-pyrrolidinocarbonyl, iso-Pr, 179.5-80°; CO2Et, iso-Pr, 84-5°; CH2CN, iso-Pr, 126-7°; CONHC4H9, iso-Pr, 113.5-14°; morpholinocarbonyl, iso-Pr, 157.5-8.5°; COEt, iso-Pr, 120-2.5°; CN, Et, 177-80°. A soln. of 40 g. IVd and 11 g. Me2NH in 250 ml. EtOH was heated 16 hrs. at 100° in a scaled system and concd. in vacuo to yield 32 g. IV.HCl.H2O (Q = NMe2, A = R = Ph, R11 = Et), m. 162-6°. The following amines were similarly prepd. and isolated as the indicated HCl or HCl.H2O salts (given Q, A, R,

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R1 for structure IV): NMe2, Ph, Ph, iso-Bu (HCl) (IVm.HCl); NMe2, Ph, Ph, PhCH2 (HCl.H2O); 2-pyrrolidinoethyl, Ph, Ph, Et (HCl.H2O); NHMe, Ph, Ph, iso-Pr (HCl); 4-methyl-1-piperazino, Ph, Ph, iso-Pr (2HCl.2H2O); 4-phenyl-1-piperazino, Ph, Ph, iso-Pr (HCl.2H2O); morpholino, Ph, Ph, iso-Pr (HCl.H2O); 2,6-dimethylmorpholino, Ph, Ph, iso-Pr (maleate); 4-carbomethoxy-1-piperazino, Ph, Ph, iso-Pr (HCl.2H2O); 2-morpholino, Ph, Ph, Et, (HCl.H2O m. 217-19°); 2-piperidino, Ph, Ph, Et; NBu2, Ph, Ph, Et, b0.05 205-10°; NMe2, Ph, cyclopentyl, Et; 2-(3,5-dimethylmorpholino), Ph, Ph, iso-Pr (maleate m. 149-50°, fumarate m. 200-3°); 2-(2,6-dimethylmorpholino), Ph, Ph, iso-Pr (maleate, m. 177-8°). Various maleates and fumarates of the above compds. were similarly prepd. IVm.HCl (10 g.) was partitioned between CHCl3 and dil. NH4OH. The CHCl3 layer was concd., the residue dissolved in MeCOEt, refluxed, treated with 4.75 g. MeBr in MeCOEt, and cooled to yield 11.5 g. IVm methobromide, m. 218-19° (MeCOEt). A soln. of 25 g. IV (Q = CN, A = R = Ph, R1 = iso-Pr) and 2 teaspoonsfuls of Raney Ni in 300 ml. abs. EtOH was shaken in a H atm. to yield 13 g. product b0.2 210-15°, which was treated with 5 g. fumaric acid to yield 6.5 g. IV fumarate (Q = CH2NH2, A = R = Ph, R1 = iso-Pr), m. 149-52°. The list of 4-ω-haloalkyl-2-pyrrolidinones given previously were converted in the manner of the preceding examples to the corresponding 4-ω-aminoalkyl-, and 4-ω-morpholinoalkyl-2-pyrrolidinones. The following representative compds. of this group were thus prepd. (structure IV, R = Ph; Q, A, R1, salt, and m.p. given): NMe2, Ph, Et, HCl.H2O, 161-4°; NBu2, Ph, Et, --, -- (b0.05 205-10°); pyrrolidino, Ph, Et, HCl.H2O, 169-72°; piperidino, Ph, Et, --, 89°; CH2NH2, Ph, iso-Pr, fumarate, 149-52°; NHMe, Ph, iso-Pr, HCl,237-9°; N-methylpiperazino, Ph, iso-Pr, 2HCl.2H2O, 185-9°; N-phenyl-piperazino, Ph, iso-Pr, HCl.2H2O, 145-51°; NMe2, Ph, iso-Bu, HCl, 154-5°; NMe2, Ph, iso-Bu, MeBr, 218-19°; NMe2, Ph, PhCH2, HCl.H2O, 181-3°; NMe2, Ph, iso-Pr, --, 94-8.5°; NEt2, Ph, iso-Pr, fumarate, 156-9°; NMe2, iso-Pr, iso-Pr, HCl, 208-10°; hexamethylenimino, Ph, iso-Pr, fumarate, 163-5°; N(Me)COMe, Ph, iso-Pr, --, 120-1°; phthalimido, Ph, iso-Pr, --, 164-6°; morpholino, Ph, Et, HCl.H2O, 217-19°; morpholino, Ph, iso-Pr, HCl.H2O, 182-5°; 2,6-dimethylmorpholino, Ph, iso-Pr, maleate, 177-8°; morpholino, Ph, iso-Pr, maleate, 173-7°; 3,5-dimethylmorpholino, Ph, iso-Pr, maleate, 149-50°; 3,5-dimethylmorpholino, Ph, iso-Pr, fumarate, 200-3°; morpholino, iso-Pr, iso-Pr, HCl, 173-6°; morpholino, Ph, iso-Pr, maleate, 155°; thiomorpholino, Ph, iso-Pr, HCl.H2O, 225-30° (decompn.); CH2NHCOMe, Ph, iso-Pr, --, 113-15°; NHCH2CH:CH2, Ph, iso-Pr, --, 103-5°; NH2, Ph, iso-Pr, --, 102-3.5°; morpholino, Ph, Me, --, 130-1°; morpholino, Ph, Et, benzoate, 123-4°; NMe2, Ph, Et, HCl,251-3° morpholino, Ph, Et, HCl,255-61.5°. The 4-(ω-haloalkyl)-3,3-disubstituted-1-substituted-2-pyrrolidinethiones (VI) corresponding to the 2-pyrrolidinones IV were prepd. by reacting the latter with P2S5. Thus, a mixt. of 150 g. IVc, 23.3 g. P2S5, and 25 g. K2S in 700 ml. dry PhMe was refluxed with stirring 24 hrs. to yield VI (Q = Cl, A = R = Ph, R1 = iso-Pr) (VIa), m. 149-51° (PhMe). The following VI compds. were similarly prepd. (given Q, A, R, R1): Cl, Ph, Ph, Et; Cl, Ph, Ph, Me; Br, Ph, Ph, Et; CN, Ph, Ph, iso-Pr, m. 166-7° (iso-PrOH); CN, Ph, Ph, Et; CN, Ph, Ph, Me; CN, Ph, Ph, cyclohexyl. A soln. of 25 g. VIa in 100 ml. morpholine was refluxed 18 hrs. to yield VI.HCl (Q = morpholino, A = R = Ph, R1 = iso-Pr), m. 275°. The corresponding Q = Et, and Q = Me compds. were prepd. similarly. Following the procedures given above for the IV compds., the following corresponding VI compds. were similarly prepd. (given Q, A, R, R1): NMe2, Ph, Ph, iso-Pr (HCl.H2O salt), m.

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196-7°; methyl-1-piperazino, Ph, Ph, iso-Pr, m. 133-4°; pyrrolidino, Ph, Ph, Et; thiomorpholino, Ph, Ph, iso-Pr; NEt2, Ph, Ph, iso-Pr (HCl salt); CO2H, Ph, Ph, iso-Pr, m. 191-4°; CO2H, Ph, Ph, Et; CO2H, Ph, Ph, Me; CO2H, Ph, Ph, cyclohexyl; COCl, Ph, Ph, iso-Pr; CO2Et, Ph, Ph, iso-Pr, m. 148.5-51°; COCl, Ph, Ph, Et; CO2Et, Ph, Ph, Et; CO2Me, Ph, Ph, Me; CO2Pr, Ph, Ph, iso-Pr; CONMe2, Ph, Ph, iso-Pr, m. 109-11°; CONEt2, Ph, Ph, Et; CONHMe, Ph, Ph, Me; CONHBu, Ph, Ph, iso-Pr; OH, Ph, Ph, iso-Pr; OH, Ph, Ph, Et; OH, Ph, Ph, Me; CO2Me, Ph, Ph, iso-Pr; CO2Et, Ph, Ph, Me; CO2Et, Ph, Ph, Et; SH, Ph, Ph, iso-Pr, b0.01 200-10°; SMe, Ph, Ph, iso-Pr; MeO, Ph, Ph, iso-Pr; MeO, Ph, Ph, iso-Bu; BzO, Ph, Ph, iso-Pr; 3-dimethylaminophenoxy, Ph, Ph, iso-Pr, m. 104-6°; COCH2CH3, Ph, Ph, iso-Pr; N-acetyl-N-methylamino, Ph, Ph, Me. Formulations are given for the prepn. of capsules, tablets, and injectable solns.

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AB The conversion by the method of King (C.A. 38, 3981) of aryl Me and methylene ketones with iodine and C5H5N or similar N-heterocyclics into phenacylpyridinium iodides (termed King reaction by the authors) was extended to quinaldine (I), lepidine (II), 9-methylacridine (III), the 3-isomeric acetylpyridines (IV), Me2CO, 2,4-(O2N)2C6H3Me (V), and p-O2NC6H4SCH2Bz (VI). The King reaction with Br and C5H5N was successful only in a few cases. It was demonstrated by the reaction with p-Me2NC6H4NO (VII) and by the King reaction that the reactivity of the methylene group increases in the order 2- and 4-picoline < quinoline, II < III, but that the reaction with alkyl halides decreases in the same order. I (5.73 g.) in 20 cc. C5H5N added to 10.15 g. iodine in 60 cc. dry C5H5N, heated 3 hrs. on the water bath, kept overnight, filtered, and the residue (12.7 g.) washed with C5H5N and recrystd. from 22 parts EtOH with C gave 1-(2-quinolylmethyl)pyridinium iodide (VIII), prisms, m. 214-16° (decomposition). I (0.01 mole), 0.001 mole iodine, and 10 cc. C5H5N kept at 20° 3 hrs. deposited VIII and I.HCl. VIII gave a blue-violet color with picryl chloride (IX) and a red (changing to brown-red) color with chloranil (X). VIII gave the HClO4 analog (Xa), prisms, m. 182-3° (decomposition) (EtOH). II yielded in the same manner 90% 4-isomer (XI) of VIII, yellowish platelets, m. 213-14° (decomposition) (EtOH). II (0.01 mole), 0.001 mole iodine, and 10 cc. C5H5N kept 7-8 hrs. at 20° gave XI and II.HCl. XI gave a blue-violet color with IX and a red color with X. XI gave a perchlorate analog, leaflets, m. 208-10° (decomposition). I (1.43 g.) in 5 cc. dry C5H5N treated with 2.55 g. iodine or 1.6 g. Br or 3.2 g. C5H5N.HBr.Br2, the resulting salt mixture dissolved in 30 cc. H2O, treated with C and then with 2N NaClO4, and the precipitate filtered off gave Xa; a series of runs was performed in this manner (reactant used, reaction temperature, reaction time in hrs., and % yield of Xa given): C5H5N.I2, 20°, 24, 89; C5H5N.I2, 100°, 3, 91; C5H5N.Br2, 20°, 3, 56; C5H5N.Br2, 20°, 24, 59.5; C5H5N.Br2, 100°, 3, 40; C5H5N.HBr.Br2, 20°, 3, 69; C5H5N.HBr.Br2, 20, 24, 68; C5H5N.HBr.Br2, 100°, 3, 47. III (3.86 g.) in 12 cc. C5H5N treated with 5.1 g. iodine in 20 cc. C5H5N, heated 3 hrs. on the water bath, filtered, and the residue washed with 25 cc. C5H5N and recrystd. from 15-18 parts 50% EtOH yielded 1-(9-acridylmethyl)pyridinium iodide (XII), yellow prisms, m. 190-1° (decomposition). XII in 30 parts H2O treated with aqueous NaClO4 and the precipitate recrystd. from 20 parts 50% EtOH gave the perchlorate analog of XII, pale yellow prisms, m. 206-8° (decomposition) with darkening from 190°. VIII (1.05 g.) in 12 cc. 50% EtOH treated at 20° with 0.5 g. VII in 12 cc. EtOH and 0.3 g. NaCN in 2 cc. H2O, diluted with an equal vol. of H2O, kept 0.5 hr. at 0°, and filtered gave 0.9 g. 2-quinolylglyoxylic acid nitrile p-dimethylaminoanil (XIII), red prisms, m. 157-8° (EtOAc). XIII (0.3 g.) in 2.5 cc. glacial AcOH and 0.2 g. o-C6H4(NH2)2 in 3 cc. 50% AcOH briefly boiled, kept 0.5 hr. on the water bath, dild. with H2O, and cooled to 0° gave 260 mg. 2-amino-3-(2-quinolyl)quinoxaline, yellow needles, m. 215.5-17° (EtOH). The p-diethylaminoanil analog of XIII, dark red prisms, m. 99-100°, was prepd. similarly. VIII (0.7 g.) in 8 cc. 50% EtOH treated with 330 mg. VII in 6 cc. EtOH, the mixt. treated at 0° with 2 cc. N NaOH and dild. with H2O, and the ppt. recrystd. from 8 parts EtOAc with C yielded 420 mg. 2-quinolinecarboxaldehyde p-dimethylaminophenylnitrone (XIV), orange-red prisms, m. 150-1.5°. Similarly was prepd. in 70% yield the 4-isomer of XIV, red prisms, m. 178-9° (3:1 C6H6-EtOH). By the method described for XIII was prepd. the 4-isomer of XIII, 93%, dark red prisms, m. 132-3° (EtOAc). 1-Methyl-2-(pyridiniomethyl)pyridinium diiodide treated in the usual manner with VII and NaCN yielded 81% 2-pyridylglyoxylic acid nitrile p-dimethylaminoanil methiodide, red brown prisms with a green metallic luster, m. 189-91° (decompn.) (abs. EtOH). I.MeI (5.7 g.) in 40 cc. dry C5H5N treated with 5.1 g. iodine in 20 cc. C5H5N, heated 10 hrs. on the water bath, kept overnight, filtered, the residue washed with 20 cc. C5H5N, dried at 60° (7.4 g.), dissolved in 10 parts 70% EtOH, treated with C, dild. with an equal vol. of EtOAc, and the ppt. recrystd. from 70 parts EtOH gave 1-methyl-2-(pyridiniomethyl)quinolinium diiodide (XV), yellow-brown prisms, m. 180-1° (decompn.); diperchlorate, prisms, m. 213-14° (decompn.). XV (490 mg.) in 10 cc. H2O treated at 20° with 0.2-0.4 cc. piperidine or 2-3 cc. N NaOH and filtered after 0.5 hr. at 0°, the residue washed with H2O, and recrystd. twice from 50 parts EtOH yielded 350 mg. 1-methyl-2-(pyridiniomethylene)-1,2-dihydroquinoline iodide-0.25H2O, red-brown leaflets, m. 183-4°. XV (980 mg.) in 25 cc. H2O treated with 10 cc. 2N NaOH, the mixt. warmed to dissolve the ppt., the soln. treated after 0.5 hr. with C and extd. with CHCl3, the ext. dried and evapd., and the residue (250 mg.) recrystd. from 40 parts ligroine gave 1-methyl-2-quinolone (XVI), prisms, m. 73.5-74°; the neutralized aq. phase concd. and treated with picric acid gave the adduct of methylpyridinium picrate and Na picrate, yellow needles, m. 210-11° (H2O). II.MeI with iodine-C5H5N yielded in the usual manner 94% crude 4-isomer (XVII) of XV, yellow platelets, m. 200-2° (decompn.), crystg. with 1 mole H2O; diperchlorate analog of XVII, prisms, m. 238-9° (decompn.) with previous sintering. XVII was converted in the usual manner to 96% 1-methyl-4-(pyridiniomethylene)-1,4-dihydroquinoline iodide, red-brown prisms with a green metallic luster, m. 163-4° (EtOH), which with NaOH yielded 75% 4-isomer of XVI, m. 151-2° (EtOH); picrate m. 227-9° (glacial AcOH). 2-Isomer of IV (2.42 g.) in 5 cc. dry C5H5N treated at 20° with 5.1 g. iodine in 15 cc. C5H5N, heated 3 hrs. on the water bath, stored overnight, filtered, the residue washed with C5H5N, dried (5.6 g.), and recrystd. from 18 parts EtOH with C yielded 1-(2-pyridinecarbonyl)pyridinium iodide (XVIII), cream-colored leaflets, m. 198-9° (decompn.); dark red-brown with IX, dark green with X; perchlorate analog (XIX), cream-colored prisms, m. 188-9° (EtOH). XIX treated in the usual manner with VII yielded 97% (crude) (2-pyridinecarbonyl)glyoxylic acid nitrile p-dimethylaminoanil (XX), dark red needles, m. 160-1° (EtOAc). The 3-isomer of IV gave similarly 80% (crude) 3-isomer (XXII) of XVIII, beige leaflets, m. 202-3° (decompn.) (EtOH), red-violet with IX, dark green with X; 3-isomer of XIX, leaflets, m. 191-2° (EtOH). XXI was converted in the usual manner with VII to 93% (crude) 3-isomer (XXII) of XX, red needles, m. 156-7° (3:1 C6H6-petr. ether). XXII was converted with o-C6H4(NH2)2 to 86% (crude) 2-cyano-3-(3-pyridyl)quinoxaline, needles, m. 193-4° (EtOAc). In the usual manner was prepd. from the 4-isomer of IV 57% 4-isomer (XXIII) of XVIII, cream-colored prisms, m. 168-9° (EtOH); dark red-brown with IX, dark green with X; 4-isomer of XIX, 62%, cream-colored needles, m. 154-5° (EtOH). XXIII with VII gave in the usual manner 93% (crude) 4-isomer (XXIV) of XX, dark red needles, m. 188-9° (EtOAc). XXIV with o-C6H4(NH2)2 yielded 90% (crude) 2-cyano-3-(4-pyridyl)quinoxaline, needles, m. 228-9° (EtOAc). XXII (326 mg.) in 3 cc. 50% EtOH mixed at 20° with 165 mg. VII in 3 cc. EtOH, cooled to 0°, treated with 1 cc. N NaOH, dild. dropwise with cold H2O to beginning crystn. (about 5 cc.), kept 1 hr. at 0°, and filtered yielded 120 mg. 4-pyridylglyoxal p-imethylaminophenylaldonitrone, red prisms, m. 122-3.5° (EtOAc). XXI (326 mg.) and 300 mg. m-O2NC6H4CHO in 5 cc. EtOH and 1.5 cc. H2O treated at 20° with 1 cc. N NaOH and kept 24 hrs. at 0° gave 160 mg. 1-[2-(m-nitrophenyl)-2-hydroxyethyl]pyridinium iodide, m. 207-9°; perchlorate analog, m. 159-60°. 2-Isomer of IV (2.42 g.) in 7 cc. 2-picoline and 5.1 g. iodine heated 8 hrs. on the steam bath, cooled, and filtered gave 1-(2-pyridinecarbonyl)-2-picolinium iodide (XXV), prisms, m. 188-9° (decompn.) (EtOH), dark red with IX and dark green with X; perchlorate analog, prisms, m. 140-2° (EtOH). XXV (680 mg.) in 10 cc. H2O treated with 680 mg. NaHCO3, heated 15 min. on the water bath, kept overnight, filtered, the residue washed with H2O, dried, and recrystd. from 10 parts 70% EtOH yielded 0.34 g. 2-(2-pyridyl)pyrrocoline, leaflets, m. 109-10°, which discolors slowly in light; a dil. soln. in C6H6 shows an intense, blue fluorescence in ultraviolet light. 2-Chloromethylpyridine-HCl (XXVI) (1.64 g.) and 10 cc. C5H5N heated 0.5 hr. on the water bath and cooled, the liquid phase decanted, the residue washed with Et2O and dissolved in 5 cc. EtOH, the soln. filtered with C, dild. with EtOAc, cooled to 0°, and the crystd. deposit recrystd. from 7 cc. hot EtOH gave 0.6 g. 2-(pyridiniomethyl)pyridinium dichloride-H2O, m. 197-8° (EtOH); 0.5 g. 2nd crop. XXVI (1.64 g.) and 10 cc. C5H5N heated 0.5 hr. on the water bath, kept at 0° overnight, decanted, the residue washed with Et2O and dissolved in 10 cc. H2O, the soln. added to 1.65 g. VII in 40 cc. EtOH and 2 g. NaCN in 10 cc. H2O, the mixt. kept 3 hrs. at 0°, dild. with stirring with 2 vols. H2O, and filtered yielded 1.7 g. 2-pyridylglyoxylic acid nitrile p-dimethylaminoanil (XXVII), red-brown prisms, m. 116-18° (EtOH). 4-Isomer (XXVIII) of XXVI (1.64 g.) in 10 cc. C5H5N heated 0.5 hr. on the steam bath, cooled, decanted, the residue washed with Et2O and dissolved in 8 cc. hot EtOH, and the soln. treated with C and dild. with EtOAc yielded 1.9 g. 4-[(4-pyridiniomethyl)pyridiniomethyl]pyridinium trichloride-H2O (XXIX), cream-colored prisms, did not m. 325°; the aq. soln. turns intensely red when treated with dil. aq. NaOH. XXIX with VII and NaCN gave in the usual manner 64% 4-isomer of XXVII, red-brown prisms, m. 145-6° (EtOAc). Dry Me2CO (0.29 g.) in 10 cc. C5H5N treated with 2.6 g. iodine in 10 cc. C5H5N, kept 2 days at 30-40°, and filtered yielded 1.5 g. acetonylenebis(pyridinium iodide) (XXX), rodlets, m. 230-1° (decompn.) (EtOH) (0.2 g. 2nd crop); diperchlorate, 86%, prisms, decomp. explosively at 284-5°; dipicrate, yellow needles, m. 218-22° (decompn.) (H2O). Similarly was prepd. 39% (crude) N-acetonylquinolinium iodide, yellow prisms, m. 207-9° (decompn.) (H2O or EtOH). VI (2.73 g.) in 8 cc. C5H5N and 2.6 g. iodine heated 9 hrs. on the water bath, dild. with C6H6, and the ppt. crystd. from 2 parts H2O gave 1.1 g. ω-pyridinio-ω-(p-nitrophenylthio)acetophenone iodide, yellow prisms, m. 194-6° (decompn.) (EtOH); perchlorate analog, cream-colored prisms, m. 175-7° (EtOH). V (3.64 g.) in 15 cc. C5H5N and 5.1 g. iodine in 25 cc. C5H5N heated 8 hrs. on the water bath, cooled, dild. dropwise with C6H6, mixed with 100 cc. C6H6, seeded, and the cryst. deposit (10.4 g.) dissolved in 100 cc. hot H2O, filtered with C, and repptd. with 5 g. NaClO4 in 20 cc. H2O gave 5.9 g. 1-(2,4-dinitrobenzyl)pyridinium perchlorate, leaflets, m. 157-9° (85% EtOH). 2-Isomer of IV (2.42 g.), 3.05 g. CS(NH2)2, and 5.1 g. iodine heated overnight on the water bath, the product washed with Et2O and dissolved in 15 cc. H2O, the soln. filtered with C, cooled, treated with concd. NH4OH, the ppt. filtered off, washed, and dried gave 2.7 g. 2-amino-4-(2-pyridyl)thiazole (XXXI), sand-colored prisms, m. 173-4° (50% EtOH); Ac deriv. m. 240-1°. Similarly was prepd. the 4-pyridyl isomer (3.1 g.) of XXXI, pale yellow leaflets, m. 263-5° (EtOH); it gave boiled 2-3 hrs. with Ac2O the Ac deriv., prisms, m. 320-2° (decompn.) (HCONMe2).

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1943:3993 CAPLUS
DOCUMENT NUMBER: 37:3993
ORIGINAL REFERENCE NO.: 37:704b-i,705a-c
TITLE: Halo carboxylic amides
INVENTOR(S): Katzman, Morris B.
PATENT ASSIGNEE(S): The Emulsol Corp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2290881		19420728	US	

AB By a process which may involve treating a halo carboxylic acid amide of an alc. amine such as N-β-hydroxyethyl-chloroaceta-mide with an acyl halide such as AcCl, intermediates are obtained for the preparation of assistants for the textile and related industries, as detergents, dyeing assistants, wetting, penetraling, lathering, foaming, froth flotation, insecticides and fungicides, antispattering agents, and the like. In some cases, and to some extent, the intermediates themselves have properties which adapt them, as such, for use for the purposes stated. At least most of the novel compds. have the general formula: RO-(T-NY)(m)- CO-Z-hal(. omega.), where R is an organic radical, preferably containing at least 4 C atoms, T stands for hydrocarbon, for example, alkylene or arylene such as ethylene or phenylene, Y is H, alkyl, cycloalkyl, alkoxy, aralkyl, aryl or alkylol, Z is preferably hydrocarbon, containing preferably less than 6 C atoms, hal is halogen, and m and w are whole numbers, preferably from one to four. Some of the compds. produced have the general formula RC(:O)OCH2CHZNH-COCH2-hal, where R is a hydrocarbon radical or substituted hydrocarbon radical containing at least 7 and preferably from 11 to 17 C atoms, and hal is halogen.-The radical R in the formula may be of aliphatic cycloaliphatic, aromatic or aromatic-aliphatic character, and may contain substituent groups such as amino, hydroxy, halogen, sulfate, sulfonic, phosphate, carboxyl, nitrile, and the like, but it is preferred that it be unsubstituted aliphatic or fatty and contain upward of 10 C atoms to about 18 C atoms. Z and T, likewise, may contain substituent groups such as amino, hydroxy, halogen, sulfate, sulfonic, phosphate, carboxyl, nitrile, and the like, and the sequence of C atoms therein may be interrupted by O, S, CO, NH, NR, where R is alkyl, and the like. In general, the compds. are prepared by initially treating a primary or secondary alcohol amine or alkylolamine, including corresponding polyamines, for example, mono-ethanolamine, with a halo carboxylic acid or derivative thereof under conditions such as to insure a substantial yield of amide. If the halo carboxylic acid is employed in the form of an ester, for example, Me chloroacetate, and low temps. are employed, of the order of about -10° to about +10°, excellent yields of amide are obtained. The resulting amide is then treated with an organic acid or halide thereof, particularly a higher-mol-weight organic acid or halide thereof to produce the ester. The process is preferably carried out in a nonaq. medium. Details are given of the production of the caprylic acid ester of N-β-hydroxyethyl-chloroacetamide and several other compds., and the organic radical represented by R in the general formulas may be derived from various sources such as straight-chain and branched-chain carboxylic, aliphatic, and fatty acids, satd. and unsatd., such as formic, acetic, propionic, lactic, tartaric, succinic, glutaric, glycolic, butyric, caprylic, caproic, capric, sebacic, behenic, arachidic, cerotic, erucic, melissic, stearic, oleic, ricinoleic, linoleic, linolenic, laurie, myristic, palmitic acids, mixts. of any two or more of the mentioned acids or other acids, mixed higher fatty acids derived from animal or vegetable sources, e. g., tallow, lard and oils such as coconut, rape-seed, sesame, palm kernel, palm, olive, corn, cottonseed, sardine, soybean, peanut, castor, seal, whale, shark, partially or completely hydrogenated animal and vegetable oils such as those mentioned; hydroxy and α-hydroxy higher aliphatic and fatty acids such as hydroxystearic acid, dihydroxystearic acid, α-hydroxystearic acid, α-hydroxypalmitic acid, α-hydroxylauric acid, α-hydroxy coconut oil mixed fatty acids, and the like; fatty acids derived from waxes such as beeswax, spermaceti, montan wax, and carnauba wax and carboxylic acids derived, by oxidation and other methods, from petroleum; cycloaliphatic and hydroaromatic acids such as hexahydrobenzoic acid, resinic acids, naphthenic acid and abietic acid; aromatic acids such as phthalic acid, benzoic acid, naphthoic acid, pyridinecarboxylic acids; hydroxy aromatic acids such as salicylic acid, hydroxybenzoic and naphthoic acids, etc.; and substitution and addn. derivs., particularly halogen substitution and addn. derivs. of the mentioned carboxylic substances, as, e. g., the α-chloro fatty acid derivs. such as chloroacetyl chloride, chlorobutyryl chloride, chlorinated oleic acid, and the like. Mixts. of any two or more of such acids may be employed if desired. In those cases where ethers are prepd., the org. radical is derived from alcoholates of alcs. corresponding to the acids mentioned.

L4 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1929:13254 CAPLUS
DOCUMENT NUMBER: 23:13254
ORIGINAL REFERENCE NO.: 23:1513i,1514a-b
TITLE: Dyeing cellulose esters and ethers
INVENTOR(S): Dreyfus, H.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 292180		19261214	GB	

AB Materials such as cellulose formate, acetate, propionate or butyrate, "immunized cotton," methyl, ethyl or benzyl cellulose or condensation products of cellulose with glycols or the like are dyed, printed, stenciled or otherwise colored with azo compds. containing one or more amino groups substituted by one or more aliphatic side chains each containing 2 or more OH groups but no COOH groups. Various solubilizing agents may be used and several examples are given, among which is the use of the product obtained by condensing p-nitroaniline with chlorobutylene glycol, reducing, diazotizing and coupling with α-naphthylamine, which gives golden shades capable of further development and alteration of color with different developers. Brit. 292,181 specifies the use, for similar purposes, of compds. (other than azo compds. and urea or thiourea derivs.) containing one or more e -amino groups (compds. in which an aryl dye nucleus is connected to an amino group or aliphatically substituted amino group through a side chain comprising a C atom or atoms, with or without other atoms such as N or O). Suitable compds. may be produced by the reduction of nitriles, by treating amino compds. (which may or may not contain an o-carboxylic group) or phenols with an alkylenediamine in the presence of a sulfite, or by treating a phenol or amine with an amino-alkyl halide. The dyes may be rendered more soluble by introduction of side chains containing OH groups as described in Brit. 285,968-9 (C. A. 23, 288). Processes of this kind are adapted also to dyeing of mixed goods in various effects.

L4 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1907:4096 CAPLUS
DOCUMENT NUMBER: 1:4096
ORIGINAL REFERENCE NO.: 1:983b-i,984a-i,985a-i,986a-e
TITLE: Researches on Ethers of Complex Function
AUTHOR(S): Sommelet, M.
SOURCE: Ann. chim. phys., [8] (1907), 9, 484-574
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB The author has prepared and studied a large number of mixed ethers, which contain in addition to the ether oxygen, the alc. or the ketone group. The article is divided into three parts: I. (a) Preparation of ethoxyacetic acid and some of its derivs., and a new method for preparing ethers from glycolic nitrile. (b) Synthesis of ketone-ethers. II. (a) The action of organic magnesium compds. on Et ethoxyacetate and ethoxyketones. (b) Study of the condensation of ketones and esters with a chlorine-substituted ether with a view to the preparation of ethers of glycols 1,2 and triols 1,2,3.
III. (a) Transformation of alc. ethers into saturated aldehydes. (b) Preparation of unsatd. aldehydes from ethers of glycerol. Part I. In the preparation of ethoxyacetic acid the method of Heintz (Jsb. Chemical, 1860, 314) is modified by purifying the acid by distillation in vacuo, immediately after liberating the sodium salt by acids, instead of converting it into the copper salt and decomposing this with hydrogen sulfide. Iso-Bu ethoxyacetate, C2H5O.CH2CO2C4H9, b.765 186° (corr.) Isoamyl ethoxyacetate, b.754 204-5° (corr.) Benzyl ethoxyacetate b.21 155°. Ph ethoxyacetate, b.18, 139°. Ethoxyacetic anhydride (C2H3OCH2CO)2O, made from the acid chloride and potassium salt of ethoxyacetate acid, b.25 142-3°. The nitriles of ethoxyacetic acid were made by the action of metallic cyanides on Et chlormethyl oxide, C2H5OCH2Cl, which was prepared by the action of hydrochloric acid on a mixture of formaldehyde and alc. The various metallic cyanides differ very much in their adaptability to this reaction with the nature of the metal which they contain. The best results were obtained with the silver salt; it should be added gradually to the organic haloid. Methoxyacetonitrile. CH3OCH2.CN, b. 120°. In the preparation of ethoxyacetonitrile, when the silver cyanide was added little by little to ethylchlormethyl oxide, a yield of about 70% of the theor. was obtained. Ethoxythioacetamide, C2H3OCH2CSNH2, from ethoxyacetonitrile, and alc. ammonium sulfide, crystallizes from benzine in colorless tables, m. 81°. Propoxyacetonitrile, C2H7OCH2CN, b.758 151-2°. Propxythioacetamide, C3H7OCH2CSNH2, colorless plates m. 63°. Isobutoxyacetonitrile, colorless liquid, agreeable odor, b44 80-82°. Isobutoxythioacetamide, colorless leaflets, m. 60-61°. Isoamytoxyacetonitrile, b.44 99°. The action of benzene on ethoxyacetyl chloride in the presence of aluminum chloride gives diphenylmethane. Ethoxyacetylacetone, C2H3OCH2COCH2COCH2, made by the action in the cold of sodium on a mixture of Et ethoxyacetate and acetone in the presence of benzene, is a colorless liquid, when freshly prepared; b.13 83-84°. Copper-salt, grayish blue, m. 149°. Methylethoxyacetylacetone, C2H5O CH2COC(CH3) COCH3, made by the action of Me iodide on the sodium salt of ethoxyacetylacetone at 125°, 103-105°. Ethylethoxyacetylacetone, b.15 103-105°. Ethylethoxyacetylacetone, b.15, 116°. The α-ethoxyketones were made from the nitriles by action of alkyl magnesium iodides according to the method for ketones described by E. E. Blaise. (Compt. rend., 132, 38, (1901)]. The ethoxyacetone prepared in this way gave a p-nitrophenylhydrazone (m. 102°) identical with

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that described by G. Leonardi and de Franchis (Gazz. chim. ital., 33, (1, 316) and a semicarbazone, C2H3OCH3C(CH3)NNHCONH2, m. 96° (with the Maquenne block). α-Ethoxybutanone, C2H5O CH2COCH2CH3, colorless liq., becoming yellow in the air, and developing an acid reaction. Reduces ammoniacal silver oxide, b.24 55°, b.764 146°, D 16/4 = 0.914. Semicarbazone needles, m. 87°. α-Ethoxypentanone, C2H5OCH2COC3H7, liq., peculiar odor, slightly sol. in water, b. 164-165° D 16/4 = 0.9218. Semicarbazone, fine spangles, m. 87°. α-Ethoxymethylpentanone, C2H5OCH2COCH2.CH(CH3)2, liq., b.20 73-74, D 16/4 = 0.8912. Semicarbazone, needles, m. 119°. α-Ethoxymethylhexanone, C2H5OCH2COCH2CH2CH(CH3)2, slightly yellow liq., peculiar odor, changes rapidly, b.18 92.5°. Semicarbazone, m. 89°. ω - Ethoxyacetophenon.vepsiln., C2H5OCH2COC6H5, b.21 134-136°. Oxime, prisms, m. 55°. Semicarbazone, m. 128°. Part II. The ethers of 1,2-glycols of the general formula R2COH.CH2OC2H5 were prepd. by the action of alkyl magnesium halides on Et ethoxyacetate. (See Palomaa, Chem.-Ztg., 28, 20 (Jan. 1904)). Ethoxy-methyl-2-propanol-2, (CH3)2COH.CH2OC2H5, colorless liq., slight odor, b.757 128.5-129°, D 15/4 = 0.8786. Yield about 68% of theor. Ethoxy-1-ethyl-2-butanol-2, (C2H5)2COH.CH2O.C2H5, colorless liq. with odor of a tertiary alc., slightly sol. in water, b. 754 168°, D 15/4 = 0.8961. Yield about 60% of theor. Ethoxy-1-propyl-2-pentanol 2, (C3H7)2COH.CH2O C2H5, colorless liq.; b.760 201°, D 19/4 = 0.8716. Ethoxy-1-iso-amyl-2-methyl-5-hexanol-2, (C5H11)COH.CH2OC2H5, b.25 143.144°, D 15/4 = 0.8595. Yield about 50% of the theor. Diphenylethoxymethylcarbinol, (C6H5)2COH.CH2OC2H5, slightly viscous liq., b.29 209-210°, D 19/4 = 1.094. The ethers of the 1,2-glycols of the general formula R2COH.CH2OC2H5 were prepd. by the action of an alkyl magnesium halide (R'MgX) on an α-ethoxyketone (R CO.CH2O C2H5). Ethoxy-1-methyl-2-butanol-2, mobile liq., b.763 148-149°, D 16.5/4 = 0.8825. Ethoxy-1-methyl-2-pentanol-2, C3H7.CH3COH.CH2O C2H5, b.760 167-168°, D 16.5/4 = 0.8767. Ethoxy-1-ethyl-2-pentanol-2, colorless, mobile liq., b.760 182-183°, D 16.5/4 = 0.8786. Ethoxy-1-ethyl-2-methyl-4-pentanol-2, (CH3)2CH.CH2C2H5COH.CH2OC2H5 colorless liq., b.26 97°, D 16.5/4 = 08731. Many attempts were unsuccessfully made to prep. the Et ethers of certain 1,2-glycols by a reaction between Et chlormethyl ether, ClCH2O C2H5, and a ketone in the presence of some metal, such as zinc, a zinc-copper couple or magnesium, when finally it was found that magnesium made active by the presence of a small quantity of mercuric chloride accomplished the desired result. The mechanism is probably as follows: the ketone, Et chlormethyl ether and magnesium give an addn. product, RR1C(OMgCl)CH2OC2H5; with water this gives the Et ether of the 1,2-glycol, R2COH.CH2OC2H5. Other chlor ethers give similar reactions. Besides ketones, esters may take part in the reaction giving ethers of 1,2,3 triols, but with aldehydes an equiv. reaction could not be brought about. With an ester an addn. product is probably first formed, which is then decompd. by water giving R.C(OH)(CH2OC2H5)2; in addn. there is formed as a side product an acetate, CH2(OR)2, which is probably produced according to the following equation: ClCH2OC2H5 + ClMgOC2H5 = MgCl2 + C2H3O.CH2.OC2H5. Ethoxy-1-methyl-2-octanol-2, C6H13 COH.CH3 CH2O C2H5, a liq. of feeble odor, b.11-12 102-105°, D 16.5/4 = 0.8665. Ethoxy-1-methyl-2-nonanol-2, C7H15COH.CH3CH2O C2H5, liq., b.11 118-119°, D 16.5/4 = 0.8685.

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(Breuer and Fincke, Ann., 198, 182) and in various other ways. Semicarbazone of methylethylacetaldehyde, m. 103-105°. Semicarbazone of methylpropylacetaldehyde, m. 100-102°. Ethylpropylacetaldehyde, C2H5.C3H7 CHCHO, liq. with a suffocating odor, b. 140-141°. The product with semicarbazide is viscous. Ethylisobutylacetaldehyde, liq. with an odor like its isomer, dipropylacetaldehyde, b. 154-155°. Semicarbazone, m. 97-98.5°. Methylhexylacetaldehyde, b.20 82-83°. Semicarbazone, m. 78-80, with sintering at 76°. Semicarbazone of methylheptylacetaldehyde, m. 77°. Transformation of ethers of glycerol, R COH (CH2OR')2, into unsatd. aldehydes, CH2: CR.COH. This reaction is brought about by the splitting off of two mols. of alc. from the ether by means of anhyd. oxalic or formic acid. α-Ethylacrolein, C2H5C(:CH2)COH, liq. of suffocating odor. A definite b.p. was not obtained, probably due to polymn. The two fractions 80-100° and 100-120° gave the same semicarbazone, m. 192-5°. α-Propylacrolein colorless liq., with a strong odor, b. 116°-118°. Semicarbazone, m. 182°. Oxidn. of propylacrolein with silver oxide gave α-propylacrylic acid, C3H7C(:CH2)COOH of Blaise and Luttringer (Bull. soc. chim., [3] 33, 775) establishing the constitution of the aldehyde. α-Isobutylacrolein, slightly yellow liq., with strong odor, b. 113°. Semicarbazone m. 184°. By adding bromine dissolved in chloroform to the aldehyde dissolved in the same solvent, a bromide was obtained on evapn. of the chloroform, in the form of an oily residue, which could not be distd. and which gave no definite compd. with sodium bisulphite or with semicarbazide. Oxidn. of α-isobutylacrolein gave the corresponding α-isobutylacrylic acid, C4H9C(:CH2)COOH, b.26 118-120°. α(n)Amylacrolein, b13 59°, and at about 165° with decompn. under ordinary pressure. Gives a bisulphite deriv. Semicarbazone, m. 154.5°. α(n)Hexylacrolein, slightly oily, colorless liq., b.15 = 78°. Bisulphite deriv. decomps. at 110°. Semicarbazone, m. 156°. α-(n)Octylacrolein, slightly oily liq., of characteristic odor, b.14 104.5-106°. Semicarbazone, m. 147.5°. α-Benzylacrolein, liq. with a rather strong odor, b.13, 118-120°. Semicarbazone, m. 189°.

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Ethoxy-1-methyl-2-undecanol-2, 9CH19COH.CH3.CH2O C2H5, colorless liq., slightly oily, feeble odor, b.12 152-153°, D 16.5/4 = 0.8623. Di-Et ether of ethylglycerol, C2H5 COH (CH2O C2H5)2, liq., b.20 84.86°, b.765 195° (corr), D 16.5/4 = 0.9503. Di-Et ether propylglycerol, liq., b.16 97°, D 16.5/4 = 0.9195. Di-Et ether of isobutylglycerol, colorless liq. b.23 111-112°, at 215° under ordinary pressure, D 16.5/4 = 0.9077. Di-Pr ether of isobutylglycerol, from Pr isovalerate and chlormethyl Pr ether, colorless oil, b.22-23 139-140°, D 16.5/4 = 0.8938. Diisobutyl ether of isobutylglycerol, oily liq. of peculiar odor, b.16 145-147°, D 16.5/4 = 0.8766. Diisoamyl ether of isobutylglycerol, colorless liq. with a feeble amyl alc. odor, b.12 162°, D 16.5/4 = 0.8785. Di-Et ether of n-amylglycerol, colorless oil with a feeble odor, b.13 118-119°, D 16.5/4 = 0.9029. Di-Et ether of n-hexylglycerol, colorless, almost odorless, oily liq., b.13 135-136°. Di-Et ether of n-decylglycerol, colorless, odorless, oily liq., b.12 180°, D 16.5/4 = 0.9. Di-Et ether of n-octylglycerol, oil, b.15 160°, D 16.5/4 = 0.8949. Di-Et ether of benzylglycerol, from Et phenylacetate, is a slightly oily liq., b.14, 174°, D 16.5/4 = 1.0091. Part III. Formation of aldehydes from compds. contg. the group, COH-CH2OR. Under the influence of various dehydrating agents, ethers of primary-tertiary glycols of the general formula R2COH-CH2OC2H3, suffer a transformation which is entirely comparable to that which takes place in an α-glycol under similar conditions. Just as the α-glycols lose a mol. of water and form satd. aldehydes, the ethers lose a mol. of alc. RR'COHCH2OH → H2O+RR'CHCHO; RR'COH.CH2OC2H5 → C2H5OH+RR'CHCHO. This decompn. takes place easily with ethers of low mol. wt. Distn. in the presence of an aq. soln. of mineral acid is sufficient to bring it about, but in almost all cases the result is very advantageous, if one employs as the dehydrating agent either crystallizable formic acid or anhyd. oxalic acid. With oxalic acid a certain amt. of Et oxalate is formed. The decompn. of these ethers by oxalic acid proceeds most easily with those of low mol. wt.; thus heating for two hours at a temp. of 110°-115°, suffices to transform dimethylethoxymethylcarbinol almost completely into isobutyric aldehyde, while four or five hours heating at 120°-125° is required to bring about a similar change in diisoamylethoxymethylcarbinol. The decompn. is facilitated by an excess of oxalic acid, and one employs in general two mols. of the latter to one of the ether. Crystallizable formic acid is more favorable than oxalic acid to the decompn. of the ethers of higher mol. wt. Isobutyric aldehyde and diethylacetic aldehyde, (C2H5)2 CH.CHO, were made with oxalic acid. The latter is a colorless liq., with a suffocating odor, easily oxidizable in the air, b.752 116°.5-118°, D 17/4 = 0.8085. Oxime, oily liq., b.34 = 95°. Semicarbazone, m. 93-94°. Dipropylacetaldehyde, (C3H7)2 CH.CHO, colorless liq. with a peculiar odor. b. 159-161° D 15/4 = 0.8347. Oxime colorless liq., b.47 = 126°. Semicarbazone, easily sol. in alc. or benzene, m. 100°-101°. Diisoamylacetaldehyde, (C5H11)2CH.CHO, colorless liq., sweet odor, b.11 103-105°, D 15/4 = 0.8261; exposed to air it is transformed by oxidn. into the cryst. diisoamylacetic acid. Oxime, liq., b.29 = 153°, acetic anhydride gives a nitrile b.19 = 129-131°. Diphenylacetaldehyde, (C5H5)2CHCHO, was obtained from diphenylethoxymethylcarbinol; it is identical with the diphenylacetaldehyde obtained from hydrobenzoin with sulfuric acid,

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